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PHYTOCHEMICAL PROFILING AND MULTI-TARGETED ANTIBACTERIAL MECHANISMS OF *CALOTROPIS PROCERA*: A REVIEW ON ITS POTENTIAL AGAINST MULTIDRUG-RESISTANT PATHOGENS

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ABSTRACT

Across the arid regions of the globe, *Calotropis procera* (the "Sodom Apple") has long been revered in traditional medicine for its ability to heal persistent infections. Modern science is now catching up, revealing that this plant is not just a botanical survivor but a sophisticated chemical factory. This review synthesizes current evidence regarding the plant's antibacterial efficacy, highlighting how its various parts leaves, bark, roots, and latex act as natural deterrents against human pathogens [3, 4]. The antibacterial strength of *C. procera* lies in its diverse secondary metabolites, including cardiac glycosides, alkaloids, flavonoids, and terpenoids [5]. These bioactive compounds work through multi-targeted mechanisms: they disrupt bacterial cell wall integrity, inhibit protein synthesis, and interfere with DNA replication [3]. Empirical studies demonstrate significant inhibitory activity against clinical isolates such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, often showing a synergistic effect when used alongside conventional antibiotics [4].
Recent advancements in in-silico docking and GC-MS profiling have further identified specific molecules, such as coumarin derivatives and specialized alpha-amylase inhibitors, that block bacterial metabolic pathways [2, 17]. As the global crisis of multidrug-resistant (MDR) bacteria worsens, *C. procera* offers a high-potential reservoir for developing novel, bio-based therapeutic agents that are both effective and culturally accessible [3, 5].

KEYWORDS: *Calotropis procera, Antibacterial Activity, Phytochemicals, Traditional Medicine, Secondary Metabolites, Drug Resistance, Bioactive Compounds*.

INTRODUCTION

For centuries, across the sun-drenched landscapes of Africa, Asia, and the Middle East, a resilient green sentinel has stood watch over the desert sands. Known scientifically as *Calotropis procera* and colloquially as the "Sodom Apple," "Giant Milkweed," or "Aak" this perennial shrub is far more than a hardy survivor of the wilderness. This introduction explores the botanical architecture and the profound antibacterial legacy of *C. procera*, synthesizing how ancient ethnobotanical practices are being validated by 21st-century pharmacology [3, 4].

Calotropis procera belongs to the Apocynaceae family, a group notorious for producing complex, bioactive molecules. Its physical presence is unmistakable: broad, silvery-green succulent leaves, waxy lavender-tinted flowers, and a thick, milky latex that bleeds from the stem at the slightest touch. While this latex is traditionally feared for its toxicity to the eyes, it is precisely this "chemical warfare" capability that makes the plant such a

potent candidate for antibacterial research. The plant does not just exist in its environment; it dominates it, producing an array of secondary metabolites alkaloids, flavonoids, cardiac glycosides, and terpenoids designed to ward off herbivores and microbial pathogens alike [5, 9]. The human relationship with *Calotropis* is deeply rooted in history. In Ayurvedic and Unani medicine, various parts of the plant have been used to treat everything from leprosy and eczema to persistent coughs and infected wounds [3]. In many rural communities, the leaves are warmed and applied to joints to reduce inflammation, while the roots are decocted to fight internal infections [11, 20]. We are currently living in a "post-antibiotic" era where common infections once easily cured are becoming life-threatening again due to multidrug-resistant (MDR) strains like Staphylococcus aureus (MRSA) and Escherichia coli [10, 12]. *Calotropis procera* has shown remarkable efficacy against these clinical isolates. Research indicates that ethanolic and methanolic extracts of the leaves and bark often exhibit a "Minimum Inhibitory Concentration" (MIC) that rivals commercial drugs, sometimes even enhancing the effect of existing antibiotics when used in combination [12, 19]. Unlike synthetic antibiotics, which often target a single bacterial site (leading to rapid resistance), the extracts of *C. procera* contain a diverse cocktail of compounds that attack the microbe from several angles simultaneously [1, 9].

1]Membrane Disruption: Specialized terpenoids and saponins act like molecular detergents, poking holes in the lipid bilayers of bacterial cell walls, causing the cell to leak its vital contents and die [9, 16].

2]Enzymatic Inhibition: Recent studies have isolated alpha-amylase inhibitors and other proteolytic enzymes from the latex that can effectively "starve" bacteria by preventing them from processing nutrients [17].

3]Oxidative Stress: The high phenolic and flavonoid content provides a dual action—while they act as antioxidants in human cells, they can induce lethal oxidative stress in bacterial pathogens [7, 11].

ANTIBACTERIAL RESISTANCE

The modern medical world is currently locked in an invisible arms race, one where the adversaries are microscopic, rapidly evolving, and increasingly indifferent to our most potent chemical defenses. Antibacterial Resistance (ABR) has transitioned from a theoretical concern of the mid-20th century to a defining global health crisis of the 21st. As bacteria like Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli develop sophisticated mechanisms to evade traditional antibiotics, the global healthcare system faces the terrifying prospect of a "post-antibiotic era" a time where routine surgeries, minor wounds, and common infections could once again become fatal [3, 4].

2.1 The Anatomy of a Crisis: Why Synthetic Drugs are Faltering

To understand why *C. procera* is so vital, one must first understand the mechanics of the enemy. Traditional synthetic antibiotics often operate as "monotherapies" they are designed to target a single, specific metabolic pathway or structural component of a bacterium, such as cell wall synthesis or protein translation. While initially effective, this singular approach provides bacteria with a clear target for evolution. Through horizontal gene transfer and rapid mutation, microbes have developed efflux pumps to "spit out" drugs, enzymes to degrade them, and altered binding sites that render the drugs useless [12, 19].

The result is a global rise in multidrug-resistant (MDR) "superbugs." These pathogens do not just survive; they thrive in hospital environments, creating a heavy burden on public health and the economy. It is estimated that without a radical shift in how we discover and apply antimicrobials, the death toll could reach 10 million

annually by 2050 [3, 4]. This urgency has pivoted the focus toward phytopharmacology, looking for "multitarget" compounds that bacteria cannot easily bypass.

2.2 *Calotropis procera*: Nature's Multitargeted Solution

Calotropis procera represents a shift from the "one drug, one target" philosophy to a "complex mixture, multiple targets" strategy. Because this plant has evolved in harsh, microbe-rich environments, it has developed a sophisticated internal defense system that does not rely on a single molecule. Instead, it utilizes a synergistic blend of alkaloids, cardiac glycosides, terpenoids, and phenolic compounds [5, 9]. When an extract of *C. procera* encounters a resistant bacterium, it attacks on multiple fronts:

. **Membrane Integrity**: Saponins and terpenoids act like molecular shears, disrupting the lipid bilayer of the bacterial cell membrane, making it porous and unstable [9, 11].

. **Efflux Pump Inhibition:** Emerging research suggests that certain flavonoids within the plant may inhibit the very pumps bacteria use to eject antibiotics, potentially "re-sensitizing" resistant strains to existing medications [12, 17].

. **Biofilm Disruption:** Many resistant bacteria protect themselves within a "biofilm"—a slimy protective layer. Components of *C. procera* latex have shown the ability to penetrate and degrade these biofilms, exposing the vulnerable bacteria underneath [13, 15].

2.3 The Path Forward: Synergy and Sustainability

As we look toward the future, the goal is not necessarily to replace synthetic antibiotics but to augment them. The concept of antibiotic synergy using *C. procera* extracts in combination with conventional drugs offers a promising path to lowering the required doses of synthetic chemicals, thereby reducing side effects and slowing the rate of further resistance [12, 16]. However, the reality of using such a potent plant involves navigating its inherent toxicity. *C. procera* is famous for its caustic latex, which requires careful processing to isolate the healing compounds from the harmful ones [13, 15]. Modern pharmacology is now focused on refining these extraction methods to ensure that the final product is safe for human systemic use.

CALOTROPIS PROCERA

3.1 Description of *Calotropis procera*

Commonly known as the "Sodom Apple" or "Giant Milkweed," *Calotropis procera* is a resilient, evergreen shrub that thrives where most life withers. Standing as a hallmark of arid and semi-arid landscapes across Africa, Asia, and the Middle East, this plant is much more than a rugged desert dweller; it is a sophisticated biological factory [3, 4]. Physically, it is distinguished by its broad, leathery, silver-green leaves that possess a waxy coating to prevent water loss, and its striking clusters of bell-shaped, white-and-purple flowers. However, its most famous and formidable feature is the thick, milky white latex that exudes from any broken tissue. This latex is a complex emulsion of enzymes and secondary metabolites, evolved primarily as a chemical defense mechanism to ward off insects and microbial invaders [5, 13]. The plant's architecture is saturated with cardiac

glycosides (such as calotropin and uscharin), alkaloids, flavonoids, and terpenoids [3, 9]. These are not merely decorative elements; they are the active "soldiers" in the plant's antibacterial arsenal [1,6].

fig.1*: calotropis procera*

3.2 Plant Anatomy and cell walls

To understand the antibacterial efficacy of *Calotropis procera*, one must look closely at its physical architecture, which is designed for extreme survival. Anatomically, the plant is a masterpiece of desert engineering. Its leaves are characterized by a thick, waxy cuticle and a dense layer of epidermal hairs (trichomes) that serve as the first line of defense against both environmental stress and microbial attachment [3, 5]. Beneath this surface lies a complex vascular system that transports its most potent weapon: a pressurized network of laticifers. These specialized elongated cells permeate the plant's tissues, storing the milky latex rich in rubber particles, resins, and bioactive proteins that exhibit immediate inhibitory effects on bacterial growth upon tissue injury [12, 13]. At the microscopic level, the cell wall of *C. procera* acts as more than just a structural boundary; it is a reservoir of antimicrobial precursors. The primary and secondary cell walls are reinforced with complex polysaccharides and lignin, which provide a rigid framework that is difficult for bacterial enzymes to penetrate [11]. Embedded within this matrix are specialized secondary metabolites, including phenolic compounds and alkaloids, which are strategically positioned to disrupt the metabolic processes of invading pathogens [3, 9].

3.3 Phytochemical constituent

The phytochemical profile of *Calotropis procera* is a sophisticated natural laboratory, rich in diverse secondary metabolites that underpin its potent antibacterial activity [1, 2]. Comprehensive screening of the leaves, roots, and latex has identified a broad range of bioactive groups, including alkaloids, flavonoids, tannins, saponins, and cardiac glycosides [2, 6]. Among these, alkaloids such as calotropin and uscharin are particularly significant; these nitrogen-containing compounds are recognized for their ability to disrupt microbial cell walls and interfere with protein synthesis in pathogens [4, 6]. Recent GC-MS profiling has further pinpointed specific high-concentration compounds like betulin (58%) and alpha-amyrin (32.87%), both of which exhibit direct bactericidal and antioxidant properties [4, 7].

3.4 Geographical Distribution

The geographical footprint of *Calotropis procera* is exceptionally expansive, reflecting its high adaptability to arid and semi-arid environments across the globe [1, 2]. Primarily native to Northern and Tropical Africa, the Arabian Peninsula, Western Asia, the Indian Subcontinent, and Indochina, the plant thrives in desert biomes and dry shrublands [1, 4]. Its resilient nature has allowed it to naturalize extensively in the Americas, spanning from the United States (California and Hawaii) and Mexico to South America (Brazil and Colombia), as well as throughout the Caribbean [1, 5]. In Australia,

C. procera has become a significant invasive species, covering approximately 3.7 million hectares of rangelands and savannahs [1].

This wide distribution is pharmaceutically significant because environmental stressors in different geographical zones directly influence the concentration of the plant's bioactive secondary metabolites [2]. These compounds, such as alkaloids, tannins, and flavonoids, are the drivers of the plant's antibacterial activity against diverse clinical pathogens [3]. Consequently, the global availability of this plant ensures it remains a vital resource for developing plant-derived antimicrobial agents capable of addressing multidrug-resistant infections [2, 3]. Consequently, the global availability of this plant ensures it remains a vital resource for developing plant-derived antimicrobial agents capable of addressing multidrug-resistant infections [2, 3].

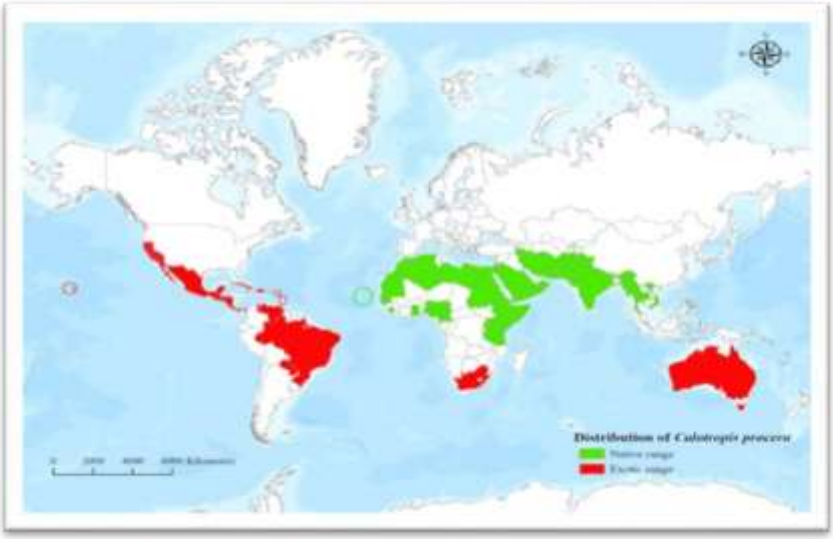

fig.2: geographical distribution

REVIEW ON EXTRACTION METHOD AND EFFICACY

The effectiveness of *Calotropis procera* as an antibacterial agent is highly dependent on the extraction methodology and the specific solvents used to isolate its bioactive compounds [1, 2]. The study indicates that organic solvents, particularly ethanol and methanol, are superior for yielding a high concentration of secondary metabolites such as alkaloids, flavonoids, and cardenolides [2, 3]. For instance, ethanolic leaf extracts have demonstrated a broad-spectrum efficacy, achieving up to 93% of the inhibitory power of standard antibiotics like amoxicillin when tested against Staphylococcus aureus [2]. Comparative studies highlight that while aqueous (water) extracts are traditional, they often show lower potency against resistant strains like Pseudomonas aeruginosa compared to their alcoholic counterparts, which benefit from the enhanced solubility of moderately polar antimicrobial constituents [1, 6].

Advanced techniques such as Soxhlet extraction are frequently reviewed as the "gold standard" for isolating specific compounds like coumarins, which contribute to the plant's ability to disrupt microbial cell membranes [3, 4]. Recent pharmacological evaluations have also focused on bioassay-guided fractionation, which has successfully isolated high-purity compounds like octadecan-2-yl acetate that exhibit superior Minimum Inhibitory Concentrations (MIC) as low as

0.63 µg/ml against methicillin-resistant pathogens [5]. Ultimately, the efficacy of these extracts whether sourced from the latex, bark, or leaves is maximized through standardized extraction protocols that ensure the stability and potency of the plant’s complex chemical matrix [1, 5].

APPLICATIONS OF *CALOTROPIS PROCERA*

The practical applications of *Calotropis procera* are as diverse as its chemical profile, bridging the gap between traditional ethnomedicine and modern clinical pharmacology [1, 2]. One of its most prominent applications is in advanced wound care; the plant's latex contains soluble proteins and cysteine peptidases that exhibit hemostatic and anti-inflammatory actions, facilitating rapid tissue regeneration while preventing bacterial colonization of the wound site. Furthermore, the processed latex and leaf extracts are being explored as antibiotic adjuvants bio-rational agents that, when combined with conventional synthetic drugs, can disrupt the defense mechanisms of multidrug-resistant pathogens like Staphylococcus aureus [2].

In the commercial and public health sectors, *C. procera* serves as a sustainable source for specialized therapeutic products. Its pungent latex is utilized in the commercial preparation of eye tonics and, when blended with honey, acts as a natural antibiotic for treating oral infections and persistent coughs. Beyond human health, the plant's essential oils are applied as green eco-friendly resources for controlling weeds and microbial growth in agricultural settings, providing a biodegradable alternative to synthetic pesticides. These broad applications, ranging from treating tropical skin diseases like leprosy to developing modern anticancer agents, highlight the plant’s essential role in both holistic healing and industrial biotechnology [2].

PHARMACOLOGICAL ROLE OF *CALOTROPIS PROCERA*

The pharmacological role of *Calotropis procera* as a potent antibacterial agent is defined by its ability to synthesize a wide array of bioactive molecules that target diverse microbial threats [1, 2]. By utilizing its rich reserves of alkaloids, terpenoids, and cardenolides, the plant effectively disrupts the physiological integrity of pathogens such as Staphylococcus aureus, Escherichia coli, and Salmonella typhi [1, 5].

A key mechanism behind this action is the presence of specialized bacteriolytic enzymes like calactin and proteolytic enzymes like calotropin, which actively degrade microbial structures [3, 4]. These compounds, particularly when concentrated in ethanolic extracts, have demonstrated inhibitory effects comparable to conventional antibiotics like ciprofloxacin and streptomycin, offering a natural strategy to bypass existing resistance mechanisms [2, 6]. Beyond direct microbial inhibition, the plant's pharmacological profile is enhanced by its dual-action capacity to reduce inflammation and oxidative stress at the site of infection [2, 3]. The latex, which contains a complex mixture of biologically active compounds such as caoutchouc and uscharin, serves not only as an antimicrobial shield but also as a therapeutic agent for skin infections and wound healing [2, 5]. This multifaceted approach combining direct bactericidal activity with the stimulation of the host's immune system establishes *C. procera* as a vital resource for modern drug discovery, particularly in the development of treatments for multidrug-resistant (MDR) infections [1, 6].

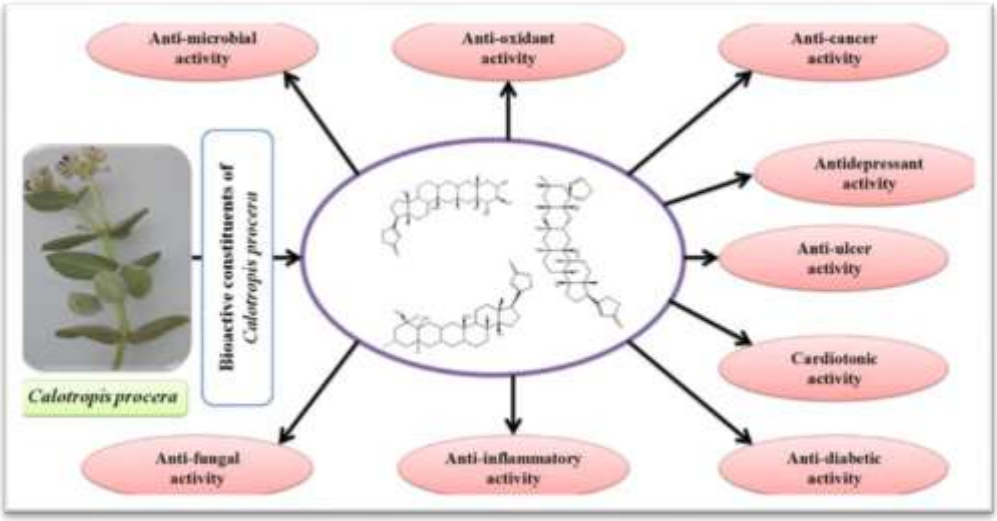

fig.3: pharmacological roles

CONCLUSION

In conclusion, *Calotropis procera* stands as a formidable biological reservoir with significant potential to reshape the landscape of antibacterial therapy [1, 2]. The plant's ability to synthesize a complex array of secondary metabolites ranging from lytic enzymes in its latex to potent alkaloids in its leaves provides a multi-targeted defense system that effectively neutralizes diverse bacterial pathogens [3, 5]. As global healthcare continues to struggle with the rise of multidrug-resistant "superbugs," the synergistic and bactericidal properties of this resilient species offer a sustainable, plant-derived alternative to traditional synthetic antibiotics [4, 6].By standardizing extraction methods and further exploring the plant's molecular docking potential, researchers can move closer to integrating *C. procera* into mainstream clinical applications, ultimately bridging the gap between ancient ethnomedicinal wisdom and modern pharmacological precision [1, 2].

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